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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,514	EATON ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,7,9 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,7,9 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0706*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 07/20/2006 has been entered.

Claims 6–7, 9 and 11–17 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Claims 6–7, 9 and 11–17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants incorporate by reference their previously submitted arguments, including those made in the Appeal Brief, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101.

The examiner incorporates by reference his previously submitted arguments, including those made in the examiner's answer, and for the reasons of record assert that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants argue that the PTO's reliance on Hu and LaBaer is also misplaced because Applicants are not relying on microarray data as discussed in Hu and LaBaer; that Applicants are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis, as evidenced by Kuo (Proteomics 5(4):894-906 (2005)), which reports "[c]omparison of microarray and proteomic expression profiles showed poor correlation. Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction [RT-PCR], Western blotting and functional assays, on several genes and proteins, nonetheless, confirmed that there is indeed good correlation between mRNA and protein expression." Applicants' arguments have been fully considered but they are not persuasive.

From the evidence provided it cannot be ascertained if Kuo's microarray data was consistent or inconsistent with Kuo's RT-PCR data. Therefore, Applicants' reliance on Kuo is misplaced.

Applicants argue that that Hu's or Labaer's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data. Applicants argue that Hu and LaBaer are silent regarding the reliability of pooled samples, and whether or not differential expression in pooled samples are susceptible to disease-independent differences between samples; that the PTO's concern that "it is unknown if the PRO874 transcript differences are disease-dependent or disease-independent" is addressed by the statement in the first Grimaldi Declaration that "DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual." (First Grimaldi Declaration at ¶ 5); that Hu and LaBaer provide no reason to expect that differential .expression in pooled samples is attributable to disease-independent differences between samples; that Hu and LaBaer do not provide a basis for doubting Applicants' differential expression data; that there is no evidence that one skilled in the art would question whether the differential expression of PRO874 mRNA in pooled samples was disease-dependent or disease-independent; that any challenge to the sufficiency of the data with respect to the utility of the nucleic acid is inappropriate. Applicants' arguments have been fully considered but they are not persuasive. The utility of the PRO874 polypeptide lies in its ability to differentiate normal tissue from tumor tissue. The first Grimaldi declaration states that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. This statement is in contrast to the specification's teachings, which discloses:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. Page 140, paragraph 0350.

The declaration does not provide anything specific concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. It is unknown what level of difference is being reported or how many samples were

tested. In practicing the invention some value for PRO874 polypeptide expression must be obtained in order to distinguish normal tissue from tumor tissue. Establishing a cutoff value for this distinction would be difficult unless one knows the typical degree of variation within the pool, which Applicants have not provided. There is no evidence of record concerning the normal range in PRO874 mRNA levels or PRO874 polypeptide levels. There is no evidence of record that a normal range of PRO874 mRNA or PRO874 polypeptide levels could be defined that would distinguish normal tissue from tumor tissue. Without knowledge of the typical degree of variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue. Pooled samples would also obscure the variation between samples, making the disclosed results for PRO874 polynucleotide expression less useful, accurate and informative than if results from individual samples had been provided. In fact the range of values from normal and/or tumor tissue could be so broad that it would be impossible to distinguish normal tissue from tumor tissue. Hu and LaBaer are evidence that a skilled artisan would consider the precise level of PRO874 gene expression as relevant.

Applicants argue that references which relate to static global levels of mRNA and protein across different genes are not relevant; that the PTO argues that because there is no correlation between static levels of mRNA and protein across genes, one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding change in the amount of the encoded protein; that given the different fuel efficiencies of different automobiles one could conclude that given the lack of correlation between the amount of gas in an automobile and the distance it travels, one cannot predict how far an automobile will travel based on the amount of gas in the tank. Applicants' arguments have been fully considered but they are not persuasive. Continuing with applicants' analogy, it is noted that applicants are not comparing the PRO874 polypeptide miles per gallon of PRO874 mRNA gas in a tissue sample with the PRO874 polypeptide miles per different amount of PRO874 mRNA gas in the same tissue sample. Applicants' are assuming a change in PRO874 polypeptide expression in two different cell samples without knowing the correlation between the change, if any, in PRO874 mRNA expression and the assumed change in PRO874 polypeptide expression. In the present case it is unknown what level of differences are being reported and if those differences are consistent and reproducible. Just as one could not predict the distances traveled on a gallon of

gas in two different cars without knowing the mpg in each car, one could not predict a change in protein expression in two different cell samples without knowing that the change in mRNA is associated with a corresponding change in the level of protein. Maybe if you added two gallons of PRO874 mRNA gas to the tumor cell you might travel twice as many PRO874 polypeptide miles as compared to one gallon of PRO874 mRNA gas in the normal cell, all else being equal. However, the PRO874 polypeptide miles per gallon of PRO874 mRNA gas in either the tumor cells or the normal cells is unknown. According to the first and second Polakis declarations, your PRO polypeptide miles per gallon of gallon of PRO mRNA gas may vary in tumor cells and normal cells. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the first and second Polakis declarations. In the absence of any specific data regarding PRO874 polypeptide expression, the fact that there may be a commonly understood general rule or dogma is insubstantial evidence of the diagnostic utility of the PRO874 polypeptide. Applicants have not provided any testing of PRO874 polypeptide expression. Applicants do not disclose the PRO874 polypeptide miles traveled per gallon of PRO874 mRNA gas in either the tumor cells or the normal cells. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic behavior.

Applicants submit a second Declaration by Dr. Polakis (attached as Exhibit 2) and argue that it provides facts to enable the PTO to draw independent conclusions. The second Polakis declaration has been considered. Like the first Polakis declaration, the second Polakis declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to Dr. Polakis. The MPEP makes clear, "factual evidence is preferable to

opinion testimony ... ." The MPEP also makes clear, "opinion" testimony is entitled to be considered, i.e., it is "admissible" in an ex parte proceeding. MPEP §716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things:

(1) The nature of the fact sought to be established.

(2) The strength of any opposing evidence.

(3) The interest of the expert in the outcome of the case.

(4) The presence or absence of factual support for the expert's opinion.

Unless an "expert" states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight.

The facts to be established are whether or not the disclosed change in PRO874 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO874 transcripts and a corresponding change in PRO874 polypeptides levels. The declarations do not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. According to the first Polakis declaration:

> The purpose of this research is to identify proteins that are abundantly expressed on certain tumor cells and that are either (i) not expressed, or (ii) expressed at lower levels, on corresponding normal cells. Paragraph 3.
>
> ... we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal cells. Paragraph 4.

The corresponding paragraphs from the second Polakis declaration say essentially the same thing except that instead of stating "significantly higher levels than in corresponding normal cells" the second Polakis declaration at paragraph 4 states "significantly higher levels in normal human tissue." Both the first and second Polakis declarations indicate that the data was generated using microarray analysis, which applicants' have disparaged as inaccurate. There is no evidence of record that either the PRO874 mRNA or the PRO874 polypeptide is abundantly expressed in either tumor tissue or normal tissue. Given the paucity of information regarding

PRO874 mRNA expression in tumors and the evidence in the art that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, one skilled in the art would not know if the change in PRO874 mRNA expression was disease-dependent or disease-independent, would not know if or how PRO874 polypeptide expression would change in tumors, and would have a reasonable, legitimate basis to doubt the utility of the PRO874 polypeptide. Even if the examiner were to assume that the disclosed change in PRO874 transcripts could reasonably be correlated with an assumed change in PRO874 polypeptide expression, it still could not be ascertained if the assumed change in PRO874 polypeptide expression would be disease-dependent or disease-independent because it is unknown if the change in PRO874 transcripts is disease-dependent or disease-independent. Even if the examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to first Polakis declaration, and 10% of the cases examined do not show a correlation, according to second Polakis declaration. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to the Polakis declarations.

Applicants submit Exhibits 3-13 to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide. Applicants submit Exhibits 14-20 which are alleged to report results that are contrary to references such as Haynes and Gygi and are alleged to offer indirect support for Applicants' asserted utility. Applicants submit Exhibit 21 which is alleged to also support Applicants' assertion in that Exhibit 21 reports a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated. Applicants' arguments have been fully considered but they are not persuasive. Orntoft (Mol Cell Proteomics. 2002 Jan;1(1):37-45) notes that it was only possible to compare mRNA and protein alterations in relatively few cases of well focused abundant proteins (Abstract) and that in the

few cases analyzed, mRNA and protein levels showed a striking correspondence although in some cases we found discrepancies that may be attributed to translational regulation, post-translational processing, protein degradation, or a combination of these (page 44, right column, full paragraph 2) and that it is at present unknown whether DNA copy number is one of the mechanisms behind alteration of these eleven proteins where they found a significant correlation between DNA copy number, mRNA expression, and protein level (page 45, left column, full paragraph 1). Furthermore, Ornoft clearly suggest that both transcript and protein levels need to be analyzed (page 45, left column, full paragraph 2). Unlike Ornoft, Applicants have not provided any testing of PRO874 polypeptide expression. Plus, there is no evidence of record that either PRO874 mRNA or PRO874 polypeptide is abundantly expressed in either tumor tissue or normal tissue. Ornoft does not provide any information regarding PRO874 mRNA expression, PRO874 polypeptide expression or the correlation between the two in tumor tissue and normal tissue. Thus, considered as a whole the evidence supports and is consistent with the examiner's position that the skilled artisan would not know if or how PRO874 polypeptide expression changes in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. In addition, Ornoft used gene expression and profiling techniques (microarrays and proteomics) (page 37, right column, last full paragraph) that Applicants have disparaged as inaccurate.

Futcher states:

> This validates the use of mRNA abundance as a rough predictor of protein abundance, at least for relatively abundant proteins. Fifth, for these abundant proteins, there are about 4,000 molecules of protein for each molecule of mRNA. This last conclusion raises questions as to how the levels of nonabundant proteins are regulated and suggests that protein instability, regulated translation, suboptimal rates of translation, and other mechanisms in addition to transcriptional control may be very important for these proteins. Page 7368, left column.

As indicated previously, Applicants have not provided any testing of PRO874 polypeptide abundance. It is unknown if the reported change in PRO874 mRNA is associated with a corresponding change in PRO874 polypeptide expression. Unlike Futcher there is no evidence of record that PRO874 mRNA or protein is either abundantly expressed or abundantly under-

expressed. Therefore, Futcher does not support applicants' position. Hu and LaBaer cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

Applicants' additional supporting references have also been considered. However, none of this evidence discloses anything specific regarding PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in normal tissue and tumor tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the first and second Polakis declarations.

Applicants acknowledge that the correlation between changes in mRNA level and protein level is not exact, and there are exceptions, as in Exhibit 22. However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. Applicants argue that the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." Applicants submit that the evidence of differential expression of the PRO874 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides. Applicants' arguments have been fully considered but they are not persuasive. Applicants' utility standard would mandate only a showing that it is "not implausible" that the invention will work for its intended purpose. If mere plausibility were the test for how to use a claimed invention, applicants could obtain patent rights to "inventions" based on a disclosure consisting of little more than guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor disclose how to use an invention rather than merely proposing an unproved hypothesis. As set forth in Brenner v. Manson:

> But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy."

The present disclosure is simply a starting point for further research and investigation into potential practical uses of the claimed polynucleotides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicants are not being asked to prove the asserted diagnostic utility either as a matter of statistical certainty or beyond a reasonable doubt. Rather, the facts to be established are, is the reported change in PRO874 transcripts tumor-dependent or tumor-independent and, if the reported change is tumor-dependent, is there a corresponding change in PRO874 polypeptide expression. Applicants have not provided any testing of PRO874 polypeptide expression. The specification does not establish if the disclosed change in PRO874 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO874 polypeptide, the specification does not provide some immediate benefit to the public for the PRO874 polypeptide. None of Applicants' exhibits, arguments or declarations establish if or how expression of the PRO874 polypeptide changes in tumor tissue as compared to normal tissue. Instead, Applicants merely propose a utility that is "not implausible," relying on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO874 mRNA expression and PRO874 polypeptide expression without any evidence of the expression level of the PRO874 polypeptide in tumor tissue or normal tissue. See, e.g., Brenner, 383 U.S. at 534, 148 USPQ at 695 (An invention does not have utility sufficient to satisfy § 101 until it is "refined and developed" to the point of providing a specific benefit in

currently available form.). Applicant should provide substantial evidence of a diagnostic utility unless one of skill in art would accept such utility as obviously correct. There is no indication that a skilled artisan would accept without question that the reported change in PRO874 transcripts is tumor-dependent or that the PRO874 polypeptide is differentially expressed in tumor tissue as compared to normal tissue in a manner consistent with the reported change in PRO874 transcripts. Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO874 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO874 transcripts and PRO874 polypeptide expression to argue that it is more likely than not that a change in PRO874 transcripts is correlated with an assumed change in PRO874 polypeptide expression. Without any evidence of the expression of PRO874 in tumor tissue this argument is of no avail to Applicants. Applicants' arguments, exhibits and declarations only show that it is not implausible that invention will work for its intended purpose. In view of the countervailing evidence, Applicants' arguments, exhibits and declarations are insufficient to meet the utility requirement because they are insubstantial evidence that expression of the PRO874 polypeptide changes in a manner that corresponds to the reported change in PRO874 transcripts. Although the asserted utility may be specific to the claimed invention, it is not substantial. Therefore, the claimed invention lacks a specific and substantial asserted utility.

The following is a response to the reply filed 08/25/2006:

In further support of applicants' assertions that differential mRNA levels generally lead to corresponding differential protein levels, Applicants submit a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 1). Applicants submit that the evidence and arguments of record establish that it is more likely than not that one of skill in the art would believe that because the PRO874 mRNA is differentially expressed in kidney and lung tumors as compared to their normal tissue counterparts, the PRO874 polypeptide will likewise be differentially expressed. Applicants argue that this differential expression of the PRO874 polypeptide makes the claimed polypeptides useful as diagnostic tools for cancer, particularly lung cancer. Applicants' arguments have been fully considered but they are not persuasive. The declaration

under 37 CFR 1.132 filed by Randy Scott is insufficient to overcome the rejection of claims 6–7, 9 and 11–17 for lack of utility. Dr. Scott bases his conclusions on microarray data, which applicants have disparaged as inaccurate. Further, Dr. Scott does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in any type of tissue sample. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to first and second Polakis declarations and because there are some exceptions on an individual gene basis, according to the Scott declaration. Neither the specification nor any of applicants' arguments or other evidence establish if the disclosed change in PRO874 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO874 polypeptide, the specification does not provide some immediate benefit to the public for the PRO874 polypeptide.

Claims 6–7, 9 and 11–17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue that they have established a substantial, specific, and credible utility for the claimed polypeptides and that to the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of

ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

Claims 14–17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that the standard for determining whether the specification meets the enablement requirement is to be evaluated based on whether or not the experimentation needed for one skilled in the art to practice the invention would be undue. Applicants submit that the PTO has failed to establish a prima facie basis for rejecting Claims 14-17 as lacking enablement; that the PTO has failed to make any specific findings of fact, or back up its assertions with any acceptable evidence or reasoning; that "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention;" that the PTO has not alleged that undue experimentation would be required to practice the claimed invention, only that the claimed scope of the invention is too broad; that the PTO has not offered any explanation of how the failure to disclose "any biological activity" results in one of skill in the art having to resort to undue experimentation to practice the claimed invention; that disclosure of a "biological activity" is not required for one of skill in the art to either make or use the claimed polypeptides; that the PTO provides no other basis for rejection of the Claims 14-17 aside from pointing to "disclosure of a single polypeptide;" that the specification teaches in detail how to make the claimed polypeptides, including variants thereof, and antibodies which specifically bind PRO874; that the specification discloses that antibodies to claimed polypeptides can be used in diagnostic assays to detect the expression of PRO874 in specific types of tissue; that there is significant guidance how to make and use the claimed polypeptides; that the disclosure and references cited in the

specification make clear, the production of polypeptides, polypeptide variants, and specific antibodies is a predictable and well established aspect of the biological sciences. See, e.g., In re Wands, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) (reversing the Board's decision of non-enablement and holding that as of 1980, undue experimentation was not required to make high-affinity monoclonal antibodies to a target peptide); Sutcliffe et al., Science (1983) 219:660-666 at 661-662 (teaching that "by following simple rules, one can in general select peptides that will elicit antibodies reactive with intact proteins") (attached as Exhibit 23).

Applicants' arguments have been fully considered but they are not persuasive. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. The specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO, as indicated below:

> "Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231.

Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO: 10, and possessing any and/or all underlying biological activities. The level of experimentation required to make and use such an invention is clearly beyond the level of enablement provided by the specification because the specification provides no disclosure of any biological activity of the native or naturally-occurring PRO874 polypeptide SEQ ID NO: 10.

Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 10 is essential to Applicants' claimed genus of variant polypeptides. The specification defines antibody specificity as follows:

> An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.

The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. The level of ingenuity required to make such an invention is clearly beyond that to be expected of skilled artisans. The specification does not disclose how this would be accomplished. Note that the claims are not limited to peptide fragments of the instantly disclosed SEQ ID NO: 10, as in Sutcliffe, or fusion proteins. Rather the claims encompass polypeptides that vary anywhere and everywhere from SEQ ID NO: 10, within the metes and bounds of the recited percent identity. After reading the specification, a person of skill in the art would not understand how to make the claimed genus, except for the native, naturally-occurring PRO874 polypeptide (SEQ ID NO: 10).

The examiner has provided sufficient evidence and reasoning to make a prima facie showing that Applicants' disclosure is not commensurate in scope with the claimed invention, which requires antibodies that "specifically detect the polypeptide of SEQ ID NO: 10."

Claims 14–17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that the PTO has not provided any reasoning or evidence as to how the absence of the disclosure of "biological activity" results in an inadequate description of the subject matter of Claims 14-17. Applicants fail to see how any "biological activity" of the claimed polypeptides, aside from being able to generate an antibody which can specifically detect the polypeptide of SEQ ID NO: 10, is at all relevant to an adequate description of the claimed polypeptides which are not claimed on the basis of any "biological activity." Applicants argue that in the absence of any other arguments as to why one of skill in the art would not recognize a description of the claimed invention in Applicants' disclosure, the PTO has failed to rebut the presumption that the specification satisfies the written description requirement for Claims 14-17. Applicants argue that claims 14-17 are adequately described by the specification.

Applicants maintain that there is no substantial variation within the species which fall within the scope of the rejected claims. Applicants argue that the rejected claims are analogous to the claims discussed in Example 14 of the written description training materials; that the PTO does not contest the written description support for any embodiment recited in Claims 16-17. Applicants submit that the applicability of Example 14 is not limited to polypeptides for which the biological function is known and recited, but extends to all situations where the polypeptide is useful and there is no substantial variation within the species encompassed by the claims; that the purpose of the recited catalytic activity in the example is to limit the amount of structural variation within the species; that similarly, in the instant case, claims 14-17 must share a particular "biological activity" which restricts the amount of permissible structural variation within the species; that this limitation combined with the disclosure of how to make and test the recited antibodies generated from the claimed polypeptides, along with the requirement of least 95% or 99% amino acid sequence identity, results in claimed subject matter where there is no substantial variation within the species encompassed by the claims. Applicants argue that the basic premise that a large genus can not be adequately described by a single species is simply wrong, citing In re Wallach; that the facts in Wallach are very similar to the instant case; that it is routine in the art to create polypeptides which have at least 95% or 99% sequence identity to SEQ ID NO: 10; that it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence, that, similarly, it is well within the knowledge of those skilled in the art how to determine which polypeptides can be used to make the recited antibodies; that the predictability of this structure/function combination is sufficient to place the claimed subject matter in the possession of the Applicants, and thus the claimed polypeptides are adequately described; that the Wallach opinion makes clear that there is no need to literally describe more than a single species to adequately describe a large genus where one of skill in the art recognizes that the disclosed species puts the applicant in possession of the claimed genus; that the PTO has failed to meet its "initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common

attributes or features of the elements possessed by the members of the genus." Applicants' arguments have been fully considered but they are not persuasive.

The specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO, as indicated below:

> "Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231.

Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO: 10, and possessing any and/or all underlying biological activities. However, the specification does not describe any biological activity of the native or naturally-occurring PRO874 polypeptide SEQ ID NO: 10.

The examiner disagrees with the premise that making the claimed variant polypeptides and is just as predictable and easy as creating all the nucleic acid molecules that encode a particular amino acid sequence. All nucleic acid molecules that encode a particular amino acid sequence all share the same property of encoding that amino acid sequence. The nature, type and number of nucleotide changes are discernable and predictable. However, the claimed variant polypeptides are all different polypeptides. The claims encompass polypeptides that vary anywhere and everywhere from SEQ ID NO: 10, within the metes and bounds of the recited percent identity. Note that the claims are not limited to fusion proteins. Unlike a biological activity, which imposes limitations on the nature, type and number of amino acid changes, the functional property of "can be used to generate an antibody ... to specially detect the polypeptide of SEQ ID NO: 10" does not limit the variation in the structure SEQ ID NO: 10 —the structure of the claimed variants — in any discernable, predictable or disclosed manner. Because the specification does not describe any biological activity of the claimed polypeptides and because the claims are not limited to any specific biologic activity of the claimed polypeptides, the present claims are not analogous to example 14 of the written description guidelines.

Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 10 is essential to Applicants' claimed genus of variant polypeptides. The specification defines antibody specificity as follows:

> An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.

The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. Therefore, the function of the claimed variants is not related to the structure of the claimed variants. Therefore, skilled artisans would not recognize the disclosure of SEQ ID NO: 10 as putting Applicants in possession of the claimed genus.

Claims 6–7, 9 and 11–17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that the specification states that "it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides;" that Figure 10 and SEQ ID NO:10 show 8 methionine residues in the sequence; that combining the statement in paragraph [0196] with the disclosure of SEQ ID NO:10, Applicants have conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicants were in possession of polypeptides of SEQ ID NO: 10 beginning at any of the methionine residues listed in SEQ ID NO:10; that one of the these polypeptides is the one which begins with the methionine at residue #34; that therefore, Applicants were clearly in possession of "the polypeptide having the amino acid sequence of amino acids 34-321 of SEQ ID NO: 10" at the time of filing; that applicants have also described in Figure 9, SEQ ID NO:9 and the cDNA deposited under ATCC accession number 209922, a cDNA sequence which encodes the entirety

of the polypeptide of SEQ ID NO: 10; that as such, SEQ ID NO:9 inherently discloses the coding sequence of the polypeptides of SEQ ID NO:10 which start at any of the eight methionine residues, including the polypeptide which begins at methionine #34; that one of skill in the art would clearly recognize that methionine #34 is encoded by the codon beginning at nucleotide 100 of SEQ ID NO:9, and that the stop codon ends at nucleotide 966; that therefore, the polypeptide of SEQ ID NO:10 which begins at residue #34 is encoded by nucleotides 100-966 of SEQ ID NO:9 and cDNA deposited under ATCC accession number 209922; that applicants were therefore clearly in possession of "the amino acid sequence of the polypeptide encoded by nucleotides 100-966 of the cDNA deposited under ATCC accession number 209922" at the time of filing; that the PTO acknowledges that paragraph [0196] discloses that methionine residues upstream or downstream of the amino acid in position 1 may be the start amino acid; that however, the PTO appears to argue that because there is more than one methionine residue in SEQ ID NO:10, Applicants have not adequately described any of the possible polypeptides of SEQ ID NO: 10 beginning at a methionine residue; that the PTO states that "the species methionine residue #34 as the starting amino acid is not supported by this generic disclosure because there is no express, implicit, or inherent support for this species to the exclusion of all the other species. In other words, there is no evidence that the disclosure would reasonably lead the skilled artisan to this particular species." Applicants submit that this argument misstates the test for compliance with the written description requirement; that the test is "whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed;" that clearly, as discussed above, at the time of filing Applicants were in possession of the polypeptide of SEQ ID NO:10 starting at methionine #34 and the nucleic acid sequence which encodes this polypeptide; that contrary to the PTO's assertion, where Applicants have adequately described several polypeptides related to SEQ ID NO:10, there is nothing in the written description requirement which prevents the Applicants from claiming only one of them; that therefore, Applicants submit that the PTO has failed to meet its initial burden of "presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims" with regard to this subject matter. Applicants' arguments have been fully considered but they are not persuasive. The species methionine residue #34 as

the starting amino acid is not supported by the generic disclosure because there is no express, implicit, or inherent support for this species to the exclusion of all the other species. There is no evidence of record that the naturally occurring PRO874 polypeptide actually starts at methionine residue #34. Therefore, the specification does not convey with reasonable clarity that Appellants were in possession of the invention now claimed. The limitation introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. 112.

Applicants argue that Figure 10 discloses the following fragments of SEQ ID NO:10: amino acids 57- 80, 110-126, 215-231, and 254-274; that implicit in the disclosure of fragments 57-80 and 110-126 of SEQ ID NO:10 is the disclosure of the fragment 81-109 of SEQ ID NO:10; that likewise, the disclosure of fragments 110-126 and 215-231 of SEQ ID NO: 10 implicitly discloses the fragment 232-253 of SEQ ID NO:10; that therefore, in light of Figure 10, Applicants were clearly in possession of the subject matter "the polypeptide having the amino acid sequence of amino acids 81-109 or 232-253 of SEQ ID NO: 10" at the time of filing; that the PTO argues that while Figure 10 discloses that SEQ ID NO:10 possesses several transmembrane domains, the extracellular domains depend on how the polypeptide is arranged in the membrane, and that the amendments imply that "81-109" and "232-253" are the extracellular domains; that the PTO concludes that "[s]upport for the one arrangement implied by the present limitations cannot be found in the disclosure as originally filed. Hence, the newly added limitations constitute new matter." Applicants submit that this rejection is improper because it is a rejection not of the subject matter that is claimed, but rather what the PTO believes is "implied" by the claims; that the disputed portion of the claims reads "An isolated polypeptide comprising:... (b) the amino acid sequence of the polypeptide having the amino acid sequence of amino acids 81-109 or 232-253 of SEQ ID NO: 10;" that nothing in this claim suggests or implies that the claimed portions of SEQ ID NO: 10 are intracellular, extracellular or transmembrane portions of the protein. Applicants remind the PTO that the test for written description on which a new matter rejection is based is "whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." Applicants argue that the PTO is improperly reading limitations into the claim that are not present, and its rejection is therefore improper since it is not directed to the claimed subject matter, but to what the PTO feels is "implied" in the

claims; that in the absence of any other arguments as to why one of skill in the art would not recognize a description of the claimed invention in Applicants' disclosure, the PTO has failed to rebut the presumption that the specification satisfies the written description requirement with respect to this subject matter. Applicants' arguments have been fully considered but they are not persuasive. The specification describes an isolated PRO polypeptide having at least about a recited % "amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein." Page 8, 0014. See also page the paragraph bridging pages 28-29. The specification also describes "an isolated PRO polypeptide which is ... transmembrane domain-deleted" (page 9, 0017). However, the specification does not specifically define the 81-109 and 232-253 fragments of SEQ ID NO: 10 as either intracellular domains or an extracellular domains. Figure 10 discloses four transmembrane domains. Thus, the extracellular domains depend on how the polypeptide is arranged in the membrane. However, the specification does not disclose how the polypeptide is arranged in the membrane. The disclosure at page 8, paragraph 0014 and at the paragraph bridging pages 28-29 coupled with figure 10 and the newly added claim limitations, imply that the 81-109 and 232-253 fragments of SEQ ID NO: 10 are extracellular domains. The only specific disclosure of a fragment of a PRO polypeptide is in the context of an extracellular domain with or without the signal peptide. The specification does not disclose a specific fragment or fragments of the PRO polypeptide that is/are the intracellular or the extracellular domain or domains. Thus, the specification does not support the claiming of the 81-109 and 232-253 fragments of SEQ ID NO: 10. Hence, the newly added limitations constitute new matter, which introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. 112.

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under

37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
NOVEMBER 12, 2006